

**Endothelin-1 (ET-1) and its receptors on haemorrhoidal tissue: A potential site for therapeutic intervention**Michael R. Dashwood<sup>a</sup>, Varut Lohsiriwat<sup>b,c</sup>,  
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Objectives: Haemorrhoids is a common anorectal condition that affects millions worldwide. We studied the potential role of ET-1 and its (ETA and ETB) receptors in haemorrhoid tissue. Methods: ET-1, ETA and ETB receptor localisation was studied in haemorrhoids using autoradiography and immunohistochemistry. Protein expression was compared between haemorrhoids and normal rectal submucosa using Western blot analysis. ETA and ETB receptor antagonist effects on ET-1- and sarafotoxin 6a-induced contraction of human mesenteric artery and vein were assessed by myography. Results: There was dense [125I]-ET-1 binding to haemorrhoidal sections with ETB > ETA binding ( $12.7 \pm 3$  vs  $4.4$  dpm  $\times$  103/mm<sup>2</sup>,  $n = 3$ , NS). Immunohistochemistry revealed a higher ETB than ETA receptor immunostaining in haemorrhoidal than in control rectal tissue. This was confirmed by Western blot analysis where haemorrhoidal ETB receptor protein levels were about 4-times higher than ETA receptors ( $78.3 \pm 28.0$  vs  $18.8 \pm 3.6$  densitometric units,  $p = 0.026$ ). ETA and ETB receptors were localised to smooth muscle of mesenteric arteries and veins with ETB receptors also on endothelium. Myograph studies showed that the sensitivity and maximum contractile response to ET-1 and sarafotoxin 6a were greater in mesenteric veins than in arteries ( $p < 0.05$ ). Conclusions: ETA and ETB receptors are present in haemorrhoids with ETB receptors predominating. Mesenteric veins are more sensitive than arteries to ET-1-induced contraction, an effect that is blocked to a greater extent by ETB compared with ETA receptor antagonists. Since ETB receptors are located on smooth muscle of both the mesenteric artery and vein ETB agonists may have therapeutic potential via a constrictor action on haemorrhoidal blood vessels.

doi:[10.1016/j.lfs.2013.12.057](https://doi.org/10.1016/j.lfs.2013.12.057)**Endothelin-1 modulates bile secretory function in rats**

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Study was conducted in acute trials on rats anaesthetized with urethane 100 mg/100 g of body weight. Endothelin-1 0.1  $\mu$ g/100 g was injected into the portal vein and 0.9% NaCl (100  $\mu$ l/100 g) was administered to the control animals. Choleresis was estimated in microlitres, each for 10 min, during a three-hour experiment. Six half-hour bile samples were collected. Concentration of the bile acids, and lipids in bile was determined by thin-layer chromatography. Endothelin-1 in vasoactive concentration (0.1  $\mu$ g/100 g) decreased choleresis with maximum reduction by 15.5% ( $p < 0.05$ ) in 40 min following its administration and exhibited diverse effects on concentration of different bile acids. Taurocholic acid was gradually reduced in control and experimental animals, but its level was higher by 9.3% ( $p < 0.05$ ) in the sixth sample of experimental animals. Concentration of glycocholic acid was reduced in the control animals, but increased following endothelin-1 administration by 12.3% ( $p < 0.05$ ),

19.7% ( $p < 0.01$ ), and 16.3% ( $p < 0.01$ ) in the last three bile samples correspondingly. Endothelin-1 caused an increase of free bile acids. Concentration of cholic acid increased in the third and sixth samples by 20.6% and 19.8% ( $p < 0.05$ ) respectively. Phospholipids increased in the fifth bile sample in endothelin-1 action by 16.7% ( $p < 0.05$ ). Free cholesterol decreased slightly but ether-coupled cholesterol increased in the last two samples by 43.8% ( $p < 0.05$ ) and 45.7% ( $p < 0.05$ ) respectively. Triglycerides increased gradually and 50% ( $p < 0.05$ ) elevation was found in the fourth bile sample. So endothelin-1 intensifies conjugation of the free bile acids and biosynthesis of ether-coupled cholesterol, trihydroxylolane acids and phospholipids in liver that assist in the improvement of bile colloidal system characteristics.

doi:[10.1016/j.lfs.2013.12.058](https://doi.org/10.1016/j.lfs.2013.12.058)**Endothelin system in intestinal villi: A possible role of endothelin-2 in the maintenance of intestinal architecture**Mariana Bianchi<sup>a</sup>, Javier Adur<sup>a</sup>, Satoshi Takizawa<sup>b</sup>,  
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The endothelin system consists of three ligands (ET-1, ET-2 and ET-3) and at least two receptors (ETA and ETB). In intestinal villi, fibroblast-like cells express endothelin receptors and response to ET-1 and ET-3 peptides, changing their cellular shape. Several functions have been attributed to these peptides in the "architecture" maintenance of intestinal villi acting over sub-epithelial fibroblasts. Despite this, ET-2 has not been analyzed in depth. In this work we show the intestine gene expression and immunolocalization of ET-1, ET-2 and ETA and ETB receptors from the duodenum to the rectus and in the villus-crypt axis in mice, allowing a complete analysis of their functions. While ET-1 is expressed uniformly, ET-2 had a particular distribution, being higher at the bottom of the villi of the duodenum, ileum and jejunum and reverting this pattern in the crypts of the colon and rectus, where the higher expression was at the top. We postulated that ET-2 would act in a cooperative manner with ET-1, giving the villus the strength enough to withstand mechanical stress.

doi:[10.1016/j.lfs.2013.12.059](https://doi.org/10.1016/j.lfs.2013.12.059)**Vasoprotective effect of endothelin receptor antagonist in ovariectomized female rats**Kento Kitada<sup>a,b</sup>, Mamoru Ohkita<sup>b</sup>, Yasuo Matsumura<sup>b</sup><sup>a</sup>*Department of Pharmacology, Kagawa University, Kagawa, Japan*<sup>b</sup>*Laboratory of Pathological and Molecular Pharmacology, Osaka University of Pharmaceutical Sciences, Osaka, Japan*E-mail address: [kento-k@med.kagawa-u.ac.jp](mailto:kento-k@med.kagawa-u.ac.jp) (K. Kitada)

The effects of hormone replacement therapy with estrogen on cardiovascular disease in post menopausal women are still controversial. We previously reported that endothelin (ET)-1/ET receptor system is involved in sex differences in the development of neointimal formation after vascular injury. In the present study, we hypothesized that dual ETA/ETB receptor antagonist (ERA) could exhibit vasoprotective effects after menopause. To confirm it, we